

Hemostatic strategies for minimizing mortality in surgery with major blood loss

Pär I. Johansson

Regional Blood Bank, Section for Transfusion Service, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Correspondence to Pär I. Johansson, MD, MPA, Medical Director, Regional Blood Bank, Section for Transfusion Service, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
Tel: +45 23729202; fax: +45 35390038; e-mail: per.johansson@rh.regionh.dk

Current Opinion in Hematology 2009, 16:509–514

Purpose of review

Continued hemorrhage remains a major contributor of mortality in massively transfused patients and controversy regarding their optimal management exists. This article reviews recent advances that impact the use and effectiveness of massive transfusion.

Recent findings

In the past 18 months, nine retrospective studies and three before and after studies have evaluated the implementation of massive transfusion protocols in massively transfused patients receiving more than 10 units of red blood cells (RBCs) within 24 h from arrival. All studies demonstrate that patients receiving a high fresh frozen plasma (FFP):RBC or platelet:RBC ratio have improved survival, with patients receiving both high FFP:RBC and platelet:RBC ratios exhibiting the highest survival rate. When whole blood thrombelastography is used to guide transfusion therapy in massively bleeding patients, an increase in FFP and platelet to RBC ratio is also seen, and this is associated with improved survival. This indicates that thrombelastography is better than conventional coagulation assays to monitor coagulopathy and predict transfusion requirements in massive bleeders.

Summary

Implementation of more aggressive hemostatic resuscitation strategies in massively bleeding patients seems reasonable, and optimally, thrombelastography should be used to monitor coagulopathy and guide FFP and platelet transfusions.

Keywords

coagulopathy, fresh frozen plasma, massive transfusion, platelets, thrombelastography, trauma

Curr Opin Hematol 16:509–514
© 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins
1065-6251

Introduction

Persistent hemorrhage remains a major contributor to mortality in massively transfused patients, of whom many develop coagulopathy [1••]. In traumatically injured patients, coagulopathy may already be present on admission of the most seriously injured patients and is associated with a poor outcome [2••]. Existing guidelines advocate early administration of crystalloids and colloids in conjunction with transfusion of red blood cells (RBCs) [3]. Guided by these guidelines, fresh frozen plasma (FFP) and platelets should only be administered when a whole blood volume or more has been substituted, and then according to conventional coagulation analyses.

The current transfusion guidelines are now being challenged, and the concept of hemostatic resuscitation, that is, providing large transfusions of RBCs, FFP, and platelets to critically injured patients in an immediate and sustained manner, has been proposed [4,5]. Furthermore, the introduction of the cell-based model of hemostasis [6] has renewed the interest in whole blood-based visco-

elastical assays for monitoring coagulopathy, instead of the conventional plasma-based coagulation analyses [7]. The purpose of the present review is to survey recent advances in the management of hemorrhage, including monitoring of coagulopathy and transfusion of blood products.

Coagulopathy associated with major blood loss

The dilution of coagulation factors and platelets is a major cause of clinical coagulopathy in massively transfused patients and a result of the recommended aggressive crystalloid resuscitation [8••]. Synthetic colloid resuscitation fluids influence coagulation competence more profoundly than do crystalloids. Hydroxyethyl starch (HES) causes a reduction in the plasma concentrations of coagulation factor VIII and von Willerbrand factor, inhibition of platelet function, and decreased interaction of activated factor XIII with fibrin polymers, effects also seen with the use of dextran [9]. In a rabbit model of uncontrolled hemorrhage, Kheirabadi *et al.* [9] demonstrated that

hemodilution with Hextend (Hospira Inc. Lake Forest, IL, USA), a HES colloid, and dextran, as opposed to albumin, resulted in hypocoagulation as evidenced by a pronounced reduction in both thrombin generation and clot strength. The reduction in clot strength corresponded to increased bleeding and high mortality, 100% (Hextend), 75% (dextran) vs. 50% (albumin) [9]. Administration of blood products also causes significant dilution due to their storage in preservatives-containing anticoagulants. Thus, even transfusion of RBCs, plasma, and platelets in a 1:1:1 ratio results in a solution with a hematocrit of 30%, coagulation factor levels of approximately 60%, and platelet levels around $80 \times 10^9/l$ [10].

Hypothermia in massively transfused patients is associated with increased risks of uncontrolled bleeding and mortality [11**]. Platelet dysfunction resulting from hypothermia occurs through multiple mechanisms of which defects in platelet adhesion and aggregation and in thrombin generation on platelets are the most important [12]. Furthermore, there is a 10% reduction in coagulation factor activity for each 1°C drop in core temperature, resulting in prolonged clotting times at temperatures below 33°C [13]. Platelet dysfunction and impaired coagulation enzyme activity are reversible with normalization of temperature to 37°C, highlighting the need to prevent and treat hypothermia aggressively.

Acidemia is induced by hypoperfusion and excess ionic chloride administered during resuscitation [11**]. Acidosis impairs essential parts of the hemostatic process; at a pH below 7.4, platelets change their shape, becoming spheres deprived of pseudopodia. The impaired thrombin generation, secondary to acidosis, is the main cause of coagulopathic bleeding, as exemplified in Martini *et al.*'s [13] experiments in which thrombin generation in the propagation phase was inhibited by a pH of 7.1 by as much as 50%. Acidemia also leads to increased degradation of fibrinogen [14]. Importantly, although acidemia can be corrected by administration of buffer solutions, this does not correct the coagulopathy, implying that the

acidotic effect is more than simply a physical reduction in protease activity.

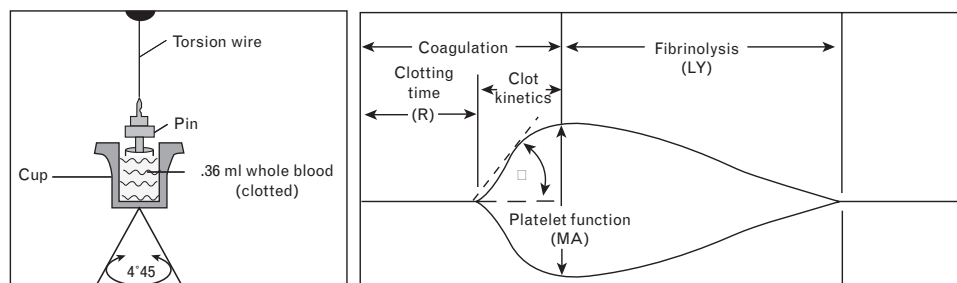
Tissue injury, particularly in association with extensive endothelial injury, is associated with consumption of coagulation factors and platelets and hence development of coagulopathy [15**]. Furthermore, there is dysregulation of coagulation attributed to consumption of antithrombin III and increased fibrinolysis due to increased levels of tissue plasminogen activator. A combination of the factors mentioned above, together with dilution, hypothermia, and metabolic acidosis, contributes to the 'bloody vicious cycle'.

Recently, Brohi *et al.* [16,17**] described an early acute coagulopathy of trauma occurring before the appearance of the aforementioned traditional causes of traumatic coagulopathy. By analyzing plasma from trauma patients, they reported that tissue injury and hypoperfusion, followed by activation of the anticoagulation thrombomodulin protein C pathway, play central roles in the pathogenesis of acute traumatic coagulopathy characterized by coagulopathy in conjunction with hyperfibrinolysis.

Monitoring hemostasis

The introduction of the cell-based model of hemostasis emphasizes the pivotal role of platelets for intact thrombin generation, and also highlights the importance of the dynamics of thrombin generation in influencing the quality and stability of the thrombus formed [6]. Consequently, hemostatic assays performed in plasma alone are of limited value, and this explains the finding that activated partial thromboplastin time (APTT) and prothrombin time (PT) do not correlate with clinically relevant coagulopathies or bleeding conditions [18,19]. Instead, it is preferable to employ a hemostatic assay, such as thrombelastography (TEG), which records the viscoelastic changes during coagulation by analysis of whole blood placed in a rotating cup [7] (Fig. 1). A pin suspended in the blood from a torsion wire records the resistance to motion. Four parameters are routinely

Figure 1 Thrombelastograph technology and measured parameters



Reproduced with permission from Johansson *et al.* [20*].

reported: reaction time (R) denotes the latency from the time at which the blood is placed in the cup until the clot begins to form, the angle (α) represents the progressive increase in clot strength, the maximum amplitude reflects the maximal clot strength, and lysis reflects clot lysis (Fig. 1).

Our group [20^{*}] demonstrated that TEG thrombus generation correlates with thrombin generation kinetics. Coagulation factor deficiency, thrombocytopenia/thrombocytopeny, or both may result in impaired thrombin formation and, in turn, impaired clot formation. Reduced clot stability, as evaluated by TEG, correlates with clinical bleeding conditions. This was elegantly demonstrated by Plotkin *et al.* [21^{**}], who reported that, in patients with penetrating trauma, TEG was a more accurate indicator of blood product requirements than PT and APTT. They recommended that TEG, enhanced by platelet count and hematocrit, should be used to guide blood transfusion requirements, and we concur with this recommendation. Furthermore, TEG is the gold standard for identifying hyperfibrinolysis, a significant cause of bleeding in major trauma, ischemia/reperfusion injury, and obstetric calamities [22,23].

The TEG analysis is now validated for routine laboratory use including with the use of the nonphysiologic activator of coagulation, kaolin, rather than with the use of tissue factor [24]. We demonstrated that the different TEG assays showed no significant day-to-day variation, and the coefficient of variance for the TEG parameters investi-

gated was acceptable for clinical practice (5–10%), also when performed on citrated blood samples. Thereby, TEG analyses can be performed in the laboratory and displayed in real-time at the bedside in the operating room, ICU, and trauma center, enabling early correction of coagulopathy by clinicians.

Administration of red blood cells

Lowered hematocrit contributes to coagulopathy. Erythrocytes are important for hemostasis by allowing marginalization of platelets toward the capillary wall and endothelium [25]. In addition, erythrocytes have been shown to modulate the biochemical and functional responsiveness of activated platelets and support thrombin generation [26]. An acute drop in the hematocrit will increase bleeding times, but this can be reversed with RBC transfusion [27^{**}]. The optimal hematocrit for platelet–vessel wall interactions is unknown but may be as high as 35% and is consequently well above the level needed for oxygen delivery [27^{**}].

Ratios of fresh frozen plasma and platelet to red blood cell

During the past 18 months, nine retrospective studies involving more than 2900 trauma patients receiving at least 10 units of RBCs within 24 h of arrival have been published [28,29^{**},30–32,33^{*},34–36]. In these studies [28,29^{**},30–32,33^{*},34–38,39^{*}], the effect on survival of administration of FFP vs. RBCs or FFP and platelets vs.

Table 1 Studies evaluating the effect of fresh frozen plasma and platelet to red blood cell ratios in 2008–2009

Author	Type of patients	No.	Type of study	Results
Duchesne <i>et al.</i> [28]	Trauma patients MT > 10 RBC/24 h	135	RC	Increased survival in patients receiving high FFP to RBC ratio
Maegele <i>et al.</i> [29 ^{**}]	Trauma patients MT > 10 RBC/24 h	713	RC	Increased survival in patients receiving high FFP to RBC ratio
Kashuk <i>et al.</i> [30]	Trauma patients MT > 10 RBC/6 h	133	RC	Increased survival in patients receiving high FFP to RBC ratio
Snyder <i>et al.</i> [31]	Trauma patients MT > 10 RBC/24 h	134	RC	Increased survival in patients receiving high FFP to RBC ratio
Teixeira <i>et al.</i> [32]	Trauma patients MT > 10 RBC/24 h	383	RC	Increased survival in patients receiving high FFP to RBC ratio
Holcomb <i>et al.</i> [33 [*]]	Trauma patients MT > 10 RBC/24 h	466 ^b	RC	Highest survival in patients receiving both high FFP and high PLT to RBC ratios
Stinger <i>et al.</i> ^a [34]	Trauma patients MT > 10 RBC/24 h	252	RC	Increased survival in patients with high FFP and PLT to RBC ratio
Perkins <i>et al.</i> ^a [35]	Trauma patients MT > 10 RBC/24 h	694	RC	Increased survival in patients receiving high PLT to RBC ratio
Zink <i>et al.</i> [36]	Trauma patients MT > 10 RBC/24 h	466 ^b	RC	Highest survival in patients receiving both high FFP and high PLT to RBC ratios
Cotton <i>et al.</i> [37]	Trauma patients MT > 10 RBC/24 h	211 ^c	RC vs. PI	PI patients received higher FFP and PLT to RBC ratios and had increased survival vs. controls
Gunter <i>et al.</i> [38]	Trauma patients MT > 10 RBC/24 h	259 ^c	RC vs. PI	Survivors received higher intraoperative FFP and PLT to RBC ratios vs. controls
Johansson <i>et al.</i> [39 [*]]	Mixed MT patients MT > 10 RBC/24 h	832	RC vs. PI	PI patients received higher FFP and PLT to RBC ratios and had increased survival vs. controls

FFP, fresh frozen plasma; MT, massive transfusion; PI, prospective intervention; PLT, platelet; RBC, red blood cell; RC, retrospective control.

^a Combat setting.

^b Included the same patients.

^c Evaluated the same patients.

RBCs has been examined (Table 1). All nine studies demonstrate a survival benefit for the patients who receive more FFP and platelets as part of the hemostatic resuscitation. This was found in both civilian and military settings. Patients receiving a high FFP:RBC or platelet:RBC ratio demonstrated improved survival, with patients receiving both high FFP:RBC and platelet:RBC ratios exhibiting the highest survival rate.

With regard to the optimal ratio of FFP:RBC, conflicting results have been reported. Maegele *et al.* [29**] showed in German trauma patients that an FFP:RBC ratio higher than 1:1 was associated with the highest survival rate. On the contrary, Kashuk *et al.* [30] reported that patients receiving an FFP:RBC ratio of 1:2–1:3 demonstrated the highest survival rate, and that a higher ratio was not associated with better outcomes but instead might actually be harmful. An important limitation on the observations reported by Kashuk *et al.* [30] is that the group receiving a high FFP:RBC ratio included only 11 patients, accounting for just 8% of the patients included in the study. It can be concluded, however, that an FFP:RBC ratio higher than 1:2 is associated with improved survival rates as compared with a ratio lower than 1:2, as is reported in five of the studies [28,30–32,33*]. Furthermore, it appears that when comparing different FFP:RBC ratios higher than 1:2, the patients receiving the most plasma exhibit the highest survival rates [29**,34].

Importantly, not only coagulation factors but also platelets are pivotal for hemostasis, and an association between thrombocytopenia and increased postoperative bleeding and increased mortality has previously been reported [5,40]. Four of the studies (Table 1) reported on the effects of platelet transfusion [33*,34–36], and all of them demonstrated improved survival in the group of patients receiving most platelets. Holcomb *et al.* [33*] demonstrated that the highest survival rate occurred in patients who received both high platelets:RBC and high FFP:RBC ratios. In fact, when comparing platelets:RBC and FFP:RBC ratios and survival rates, patients receiving a high platelets:RBC ratio displayed the highest survival rate. This is further corroborated by Stinger *et al.* [34] who reported, by multiple regression analyses, that platelet transfusion is independently associated with survival.

Massive transfusion protocols

Cotton *et al.* [37] implemented a trauma exsanguination protocol (TEP) involving 10 units of RBCs, four units of FFP, and two units of apheresis platelets for trauma patients. This protocol was used to evaluate 211 trauma patients, of whom 94 received TEP and 117 were historic controls. TEP patients intraoperatively received more RBCs (16 vs. 11), FFP (eight vs. four), and apheresis platelets (two vs. one) than the controls and displayed

Table 2 Thrombelastograph treatment algorithm for actively bleeding patients

TEG parameter	Treatment
R 11–14 min	2 × FFP or 10 ml/kg
R > 14 min	4 × FFP or 20 ml/kg
MA 46–50 mm	1 PC or 10 ml/kg
MA < 46 mm	2 PC or 20 ml/kg
Angle < 52°	2 × FFP or fibrinogen
Ly30 > 8%	Tranexamic acid

FFP, fresh frozen plasma; Ly30, lysis; MA, maximum amplitude; PC, platelet concentrate; TEG, thrombelastograph. Reproduced with permission from Johansson *et al.* [39*].

lower 30-day mortality (51 vs. 66%). After controlling for age, sex, mechanism of injury, trauma injury severity score (TRISS), and 24-h blood product usage, a 74% reduction in the odds of mortality was observed among patients in the TEP group. Overall blood product consumption adjusted for age, sex, mechanism of injury, and TRISS was also significantly reduced in the TEP group. Gunter *et al.* [38] evaluated an additional 48 TEP-treated trauma patients together with those investigated by Cotton *et al.* [37] and demonstrated that the ratio of FFP to RBCs was an independent predictor of 30-day mortality when controlling for age and TRISS (odds ratio 1.78, 95% confidence interval 1.01–3.14).

Our group investigated 832 consecutive massively transfused patients 2 years prior to and 2 years after implementation of hemostatic control resuscitation (HCR) [39*]. This protocol encompassed transfusion packages made up of five units of RBCs, five units of prethawed FFP, and two units of buffy coat platelets (produced from four buffy coats) to be administered to patients with uncontrollable bleeding. When hemodynamic control was established, the transfusion therapy was directed by TEG analyses (Table 2). The HCR group had higher FFP:RBC ratio and received more platelets within 24 h of admission as compared with controls, and the 30 and 90-day mortality was significantly reduced following HCR implementation vs. controls (20 vs. 31% and 22 vs. 35%), corroborating the results from the trauma setting.

Interestingly, Cotton *et al.* [41**] recently reported on the same cohort previously described, with inclusion of a total of 264 trauma patients, and found that not only was the 30-day survival rate higher in the TEP group than in controls but also that the incidence of severe sepsis or septic shock and multiorgan failure were lower in TEP patients (9 vs. 20% and 16 vs. 37%, respectively).

Recombinant factor VIIa

Recombinant factor VIIa (rFVIIa) acts in supraphysiological doses by enhancing thrombin generation on activated platelets independent of factor VIII and IX and is currently approved for episodes of severe hemorrhage or

perioperative management of bleeding in patients with congenital factor VII deficiency and hemophilia A or B with inhibitors [42]. Since the first case report of rFVIIa use in trauma was published in 1999 [43], there has been substantial off-label use of rFVIIa for the management of various nonhemophilic bleeding conditions. To date, 17 randomized controlled trials have been reported concerning different bleeding conditions and none have reported a survival benefit in the rFVIIa-treated arms [44]. In June 2008, Novo Nordisk discontinued a phase-3 clinical trial with NovoSeven for the treatment of bleeding in patients with severe trauma (http://www.drugs.com/clinical_trials/novo-nordisk-discontinues-phase-3-clinical-trial-novoseven-trauma-4741.html).

However, in patients with massive uncontrolled blood loss, Spinella *et al.* [45] reported a case-control study from the Iraqi combat setting in massively transfused patients with an injury severity score above 15. This study demonstrated reduced 30-day mortality in rFVIIa-treated patients as compared with controls (31 vs. 51%). Furthermore, Berkhof and Eikenboom [46] recently reported on 32 patients with uncontrolled massive blood loss, demonstrating a significant reduction in transfusion requirements after administration of rFVIIa, when compared with before administration, and a 56% survival. Importantly, administration of rFVIIa should be preceded by administration of platelets and fibrinogen to ensure optimal conditions for the rFVIIa to act. Off-label use of rFVIIa, however, is still considered controversial and should be used only with caution and sound clinical judgment.

Conclusion

Implementation of more aggressive hemostatic resuscitation strategies in massively bleeding patients seems reasonable on the basis of this review. It is intriguing that increased amounts of plasma and platelets result in improved survival, and that this is the recommended therapy when TEG is used to guide transfusion therapy in massively bleeding patients. This indicates that whole blood viscoelastic assays may be preferable for monitoring coagulopathy in massive bleeders and supports a paradigm shift in transfusion medicine regarding monitoring and treatment of massive bleeders.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 528).

- 1 Geeraedts LM Jr, Kaasjager HA, van Vugt AB, *et al.* Exsanguination in trauma: •• a review of diagnostics and treatment options. *Injury* 2009; 41:11–20. This study reviews current management of bleeding in trauma patients both in a prehospital and in an in-hospital setting.

- 2 Beekley AC. Damage control resuscitation: a sensible approach to the •• exsanguinating patient. *Crit Care Med* 2008; 36:S267–S274. An excellent review of the concepts of how to treat exsanguinating patients.
- 3 Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology* 2006; 105:198–208.
- 4 Fries D, Innerhofer P, Schobersberger W. Time for changing coagulation management in trauma-related massive bleeding. *Curr Opin Anaesthesiol* 2009; 22:267–274.
- 5 Johansson PI, Hansen MB, Sørensen H. Transfusion practice in massively bleeding patients: time for a change? *Vox Sang* 2005; 89:92–96.
- 6 Roberts HR, Hoffman M, Monroe DM. A cell-based model of thrombin generation. *Semin Thromb Hemostat* 2006; 32:32–38.
- 7 Reikvam H, Steien E, Hauge B, *et al.* Thrombelastography. *Transfus Apher Sci* 2009; 40:119–123.
- 8 Chappell D, Jacob M, Hofmann-Kiefer K, *et al.* A rational approach to •• perioperative fluid management. *Anesthesiology* 2008; 109:723–740. An important review concerning side effects of fluid therapy, emphasizing a rational approach according to the actual needs of the individual patient.
- 9 Kheirabadi BS, Crissey JM, Deguzman R, *et al.* Effects of synthetic versus natural colloid resuscitation on inducing dilutional coagulopathy and increasing hemorrhage in rabbits. *J Trauma* 2008; 64:1218–1228.
- 10 Armand R, Hess JR. Treating coagulopathy in trauma patients. *Transfus Med Rev* 2003; 17:223–231.
- 11 Lier H, Krep H, Schroeder S, *et al.* Preconditions of hemostasis in trauma: a •• review. The influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. *J Trauma* 2008; 65:951–960. An excellent review of factors influencing hemostasis in trauma patients.
- 12 Watts DD, Trask A, Soeken K, *et al.* Hypothermic coagulopathy in trauma: effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. *J Trauma* 1998; 44:846–854.
- 13 Martini WZ, Dubick MA, Wade CE, *et al.* Evaluation of tris-hydroxymethyl-aminomethane on reversing coagulation abnormalities caused by acidosis in pigs. *Crit Care Med* 2007; 35:1568–1574.
- 14 Martini WZ, Holcomb JB. Acidosis and coagulopathy: the differential effects on fibrinogen synthesis and breakdown in pigs. *Ann Surg* 2007; 246:831–835.
- 15 Hess JR, Brohi K, Dutton RP, *et al.* The coagulopathy of trauma: a review of •• mechanisms. *J Trauma* 2008; 65:748–754. An outstanding review of the relevant mechanisms influencing development of coagulopathy in trauma patients.
- 16 Brohi K, Cohen MJ, Ganter MT, *et al.* Acute traumatic coagulopathy: initiated by hypoperfusion – modulated through the protein C pathway? *Ann Surg* 2007; 245:812–818.
- 17 Brohi K, Cohen MJ, Ganter MT, *et al.* Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *J Trauma* 2008; 64:1211–1217. Brohi *et al.* [17**] demonstrate that in injured patients, consumption and dilution are not the main underlying mechanisms of trauma-induced coagulopathy. Instead, their work indicates that the presence of hypoperfusion triggers systemic endogenous anticoagulation by activating the thrombomodulin–protein C pathway, resulting in increased fibrinolysis.
- 18 Murray D, Pennell B, Olson J. Variability of prothrombin time and activated partial thromboplastin time in the diagnosis of increased surgical bleeding. *Transfusion* 1999; 39:56–62.
- 19 Segal JB, Dzik WH. Transfusion medicine hemostasis clinical trials network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion* 2005; 45:1413–1425.
- 20 Johansson PI, Bochsén L, Svendsen M, *et al.* Investigation of the thrombin • generating capacity, evaluated by thrombogram and clot formation evaluated by thrombelastography of platelets stored in the blood bank for up to 7 days. *Vox Sang* 2008; 94:113–118. This study provides a scientific rationale for why TEG, better than plasma-based hemostatic assays, correlates with clinically relevant coagulopathies by finding a correlation between the result of the TEG analysis and thrombin generation kinetics in platelet concentrates.
- 21 Plotkin AJ, Wade CE, Jenkins DH, *et al.* A reduction in clot formation rate and •• strength assessed by thrombelastography is indicative of transfusion requirements in patients with penetrating injuries. *J Trauma* 2008; 64:64–68. An important study demonstrating the superior value of TEG as opposed to conventional coagulation assays in predicting transfusion requirements in trauma patients.

- 22** Levrat A, Gros A, Rugeri L, *et al.* Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. *Br J Anaesth* 2008; 100:792–797.
- 23** Rugeri L, Levrat A, David JS, *et al.* Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. *J Thromb Haemost* 2007; 5:289–295.
- 24** Johansson PI, Bochsén L, Andersen S, *et al.* Investigation of the effect of kaolin- and tissue-factor-activated citrated whole blood, on clot forming parameters, as evaluated by thromboelastography. *Transfusion* 2008; 48:2377–2383.
- 25** Ujttewaal WS, Nijhof EJ, Bronkhorst PJ, *et al.* Near-wall excess of platelets induced by lateral migration of erythrocytes in flowing blood. *Am J Physiol* 1993; 264:H1239–H1244.
- 26** Peyrou V, Lormeau JC, Hérault JP, *et al.* Contribution of erythrocytes to thrombin generation in whole blood. *Thromb Haemost* 1999; 81:400–406.
- 27** Perkins JG, Cap AP, Weiss BM, *et al.* Massive transfusion and nonsurgical hemostatic agents. *Crit Care Med* 2008; 36:S325–S339.
- An outstanding review concerning the effect of massive transfusion and management hereof.
- 28** Duchesne JC, Hunt JP, Wahl G, *et al.* Review of current blood transfusions strategies in a mature level I trauma center: were we wrong for the last 60 years? *J Trauma* 2008; 65:272–278.
- 29** Maegele M, Lefering R, Paffrath T, *et al.* Red blood cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiply injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie. *Vox Sang* 2008; 95:112–119.
- A large retrospective cohort study of massively transfused trauma patients from the German trauma registry demonstrating the impact of FFP to RBC ratio on survival in a large cohort of patients.
- 30** Kashuk JL, Moore EE, Johnson JL, *et al.* Postinjury life threatening coagulopathy: is 1:1 fresh frozen plasma:packed red blood cells the answer? *J Trauma* 2008; 65:261–271.
- 31** Snyder CW, Weinberg JA, McGwin G Jr, *et al.* The relationship of blood product ratio to mortality: survival benefit or survival bias? *J Trauma* 2009; 66:358–362.
- 32** Teixeira GR, Inaba K, Shulman I, *et al.* Impact of plasma transfusion in massively transfused trauma patients. *J Trauma* 2009; 66:693–697.
- 33** Holcomb JB, Wade CE, Michalek JE, *et al.* Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg* 2008; 248:1–8.
- An important retrospective cohort study in massively bleeding trauma patients demonstrating that early and aggressive administration of plasma and platelets is associated with improved survival.
- 34** Stinger HK, Spinella PC, Perkins JG, *et al.* The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. *J Trauma* 2008; 64:S79–S85.
- 35** Perkins JG, Andrew P, Spinella PC, *et al.* An evaluation of the impact of apheresis platelets used in the setting of massively transfused trauma patients. *J Trauma* 2009; 66:S77–S85.
- 36** Zink KA, Sambasivan CN, Holcomb JB, *et al.* A high ratio of plasma and platelets to packed red blood cells in the first 6 h of massive transfusion improves outcomes in a large multicenter study. *Am J Surg* 2009; 197:565–570.
- 37** Cotton BA, Au BK, Nunez TC, *et al.* Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. *J Trauma* 2008; 64:1177–1182.
- 38** Gunter OL Jr, Au BK, Isbell JM, *et al.* Optimizing outcomes in damage control resuscitation: identifying blood product ratios associated with improved survival. *J Trauma* 2008; 65:527–534.
- 39** Johansson PI, Stensballe J. Effect of haemostatic control resuscitation on mortality in massively bleeding patients: a before and after study. *Vox Sang* 2009; 96:111–118.
- This study for the first time demonstrated that the concept of HCR encompassing transfusion packages and based on TEG for massively transfused patients is associated with improved survival.
- 40** Adam DJ, Haggart PC, Ludlum CA, Bradbury AW. von Willebrand factor and platelet count in ruptured abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 2003; 26:412–417.
- 41** Cotton BA, Au BK, Nunez TC, *et al.* Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. *J Trauma* 2009; 66:41–49.
- This study, for the first time, demonstrated that early and aggressive administration of plasma and platelets reduces the incidence of multiple organ failure in massively transfused patients.
- 42** Hedner U. Factor VIIa and its potential therapeutic use in bleeding-associated pathologies. *Thromb Haemost* 2008; 100:557–562.
- 43** Kenet G, Walden R, Eldad A, *et al.* Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 1999; 354:1879.
- 44** Johansson PI. Off-label use of recombinant factor VIIa for treatment of haemorrhage: results from randomised clinical trials. *Vox Sang* 2008; 95:1–7.
- 45** Spinella PC, Perkins JG, McLaughlin DF, *et al.* The effect of recombinant activated factor VII on mortality in combat-related casualties with severe trauma and massive transfusion. *J Trauma* 2008; 64:286–293.
- 46** Berkhof FF, Eikenboom JC. Efficacy of recombinant activated factor VII in patients with massive uncontrolled bleeding: a retrospective observational analysis. *Transfusion* 2009; 49:570–577.